REMARKS

Objection to Specification & Rejections under 35 U.S.C. § 112, First Paragraph

The objection to the specification and the rejection of claims 134-138 under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description and an enabling disclosure are respectfully traversed.

As described in the specification (e.g., page 13, first full paragraph), monoclonal antibodies produced by the cell lines MAB M 10.1.1 and MAB M 13.4.14 were deposited and received on the 26th of January 1999 with the DSMZ GmbH in Braunschweig, Germany. In accordance with MPEP 2405, the DSMZ (i.e., Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH) is recognized as an international depository under the Budapest Treaty.

Inasmuch as the specification already contains evidence of a deposit in compliance with 37 CFR §§ 1.801-1.809, Applicants respectfully submit that the claimed invention is fully enabled and that the written description is entirely adequate. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The written description and enablement rejections of claim 74 under 35 U.S.C. § 112, first paragraph, have been rendered moot by cancellation of this claim. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The written description and enablement rejections of claims 1-73 and 75-140 under 35 U.S.C. § 112, first paragraph, are respectfully traversed.

The definition of N-terminal proBNP provided by Applicants in the third full paragraph on page 6 of the specification would have been abundantly clear to one of ordinary skill in the art in view of the description therein. As described in the specification (e.g., page 6, second full paragraph), the claimed methods provide detection of native N-terminal proBNP in a sample which—if the molecule is intact—corresponds to N-terminal amino acids 1-76 of proBNP (e.g., specification, paragraph bridging pages 3 and 4). However, as further explained (e.g., page 6, second full paragraph; page 11, first full paragraph), the peptidic material that binds to the antibodies in the claimed methods may

correspond to a partially proteolytically digested fragment of N-terminal proBNP (i.e., a subset of the 76 amino acids) or to uncleaved proBNP (amino acids 1-76 still attached to amino acids 77-108). Since the claimed methods may not differentiate between native N-terminal proBNP (1-76), uncleaved proBNP (1-108) that includes amino acids 1-76, and breakdown products containing a subset of amino acids 1-76, Applicants have defined N-terminal proBNP to include all of the above-described related peptides that may be identified in the test procedure. Applicants respectfully submit that the definition provided in the specification fully conforms with MPEP 2111.01, which states that "[a]ny special meaning assigned to a term 'must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention.' *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998)." Applicants respectfully submit that there is no ambiguity associated with the definition of N-terminal proBNP provided in the specification and that one of ordinary skill in the art would understand this definition.

Inasmuch as all terminology recited in the claims is both described in the specification and would be well understood by those of ordinary skill in the art, Applicants respectfully submit that the claimed invention is fully enabled and that the claims reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 22, 31, 40, 49, 58, 67, 77, 86, 95, 104, 113, and 122 under 35 U.S.C. § 112, second paragraph, as being indefinite is respectfully traversed. The meaning of the claim recitation "bind simultaneously" would have been abundantly clear to one of ordinary skill in the art in view of the description in the specification.

As explained in the specification, the phrase "bind simultaneously" refers to a temporal parameter. For example, the specification states that "the epitopes are localized in a manner enabling both antibodies to bind at the same time" (page 6, second full paragraph, emphasis added).

For at least the reasons set forth above, Applicants respectfully submit that the present claims are not indefinite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 38-73 and 93-128 under 35 U.S.C. § 112, second paragraph, as being indefinite for the claim recitation "using" has been rendered moot by the rewriting of base claims 38-55. For the record, Applicants respectfully disagree with the Examiner's characterization of the word "using" in the previous versions of these claims as being an improper method step. The previous versions of these claims already recited proper method steps such as "identifying an amount of N-terminal proBNP" and "correlating the amount of N-terminal proBNP." The recitation of the word "using" in the previous versions of the claims was synonymous with the word "utilizing," a term that is not indefinite according to MPEP 2173.05(q). Nonetheless, in accordance with the Examiner's suggestion, Applicants have replaced the claim recitation "using" with the claim recitation "with" to render this rejection moot.

For at least the reasons set forth above, Applicants respectfully submit that the present claims are not indefinite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claim 129 under 35 U.S.C. § 112, second paragraph, as being indefinite has been obviated by amendment. The interrelationship of the components of the claimed method has been clarified.

For at least the reasons set forth above, Applicants respectfully submit that the present claims are not indefinite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claim 136 under 35 U.S.C. § 112, second paragraph, as being indefinite for the recitation "the antibody ... is equivalent" is respectfully traversed. The meaning of the claim recitation "the antibody ... is equivalent" would have been abundantly clear to one of ordinary skill in the art in view of the description in the specification.

For example, the specification states that "[a] further subject matter of the invention are antibodies which are like those of the cell lines M 10.1.11 and M 13.4.14 produced in an equivalent way and suitable for specifically binding to N-terminal proBNP." The specification further states that "[t]he expression 'antibodies produced in an equivalent way' means that the antibodies are obtained by immunization with recombinant N-terminal proBNP" (page 13, second full paragraph).

For at least the reasons set forth above, Applicants respectfully submit that the present claims are not indefinite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claim 140 under 35 U.S.C. § 112, second paragraph, as being indefinite has been obviated by amendment. The interrelationship of the components of the claimed method has been clarified.

For at least the reasons set forth above, Applicants respectfully submit that the present claims are not indefinite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 101

The rejection of claims 130-131 under 35 U.S.C. § 101 as being directed to non-statutory subject matter is respectfully traversed.

Claims 130-131 are directed to antibodies against recombinant N-terminal proBNP. As described in the specification, antibodies produced by immunizing an animal with recombinant N-terminal proBNP are isolated and purified (e.g., Example 2, pages 16-17; Example 3, pages 18-19). For example, as described in the specification (paragraph bridging pages 18-19), the monoclonal antibodies MAB M 10.1.11 and MAB M 13.4.14, which are specifically directed against human N-terminal proBNP, were isolated.

Inasmuch as the claimed antibodies are produced and isolated by procedures involving the "hand of man," Applicants respectfully submit that the claimed antibodies represent statutory subject matter. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 102

The rejection of claim 74 under 35 U.S.C. § 102(b) as being anticipated by *Hall* (U.S. Patent No. 5,786,163) has been rendered moot by cancellation of this claim. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 20-28 and 38-46 under 35 U.S.C. § 102(b) as being anticipated by *Hall* has been obviated by amendment. Independent claim 20 has been amended to recite a lower detection limit for the N-terminal proBNP that is less than 1 fmol/ml of sample. This lower detection limit is neither taught nor suggested in *Hall*.

Hall describes a BNP antibody and immunoassay for its use. *Hall* contains no teaching or suggestion of the lower detection limit required by the claimed invention. Moreover, as further explained below in the remarks relating to the 35 U.S.C. § 103 rejections, the competitive assays described in *Hall* exhibit lower detection limits that are significantly higher than that required by the claimed invention.

Inasmuch as *Hall* fails to teach or suggest the lower detection limit of the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this reference. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 129-133, 136, and 139 under 35 U.S.C. § 102(b) as being anticipated by *Hall* is respectfully traversed.

Independent claims 129 and 139 are directed to a method of producing antibodies against N-terminal proBNP and require "immunizing an organism with recombinant N-terminal proBNP" (emphasis added). The method of producing antibodies described in *Hall* is based on immunizations with peptide fragments of N-terminal proBNP—not with recombinant N-terminal proBNP, as required by the claimed invention. There is no teaching or suggestion in *Hall* of any desirability or advantage of immunizing an organism with recombinant N-terminal proBNP as opposed to peptide fragments thereof. However, as described in the specification (e.g., page 21), antibodies obtained via peptide immunizations exhibit substantially differently affinities for native N-terminal proBNP compared to antibodies obtained via recombinant N-terminal proBNP immunizations in

accordance with the claimed invention. Inasmuch as *Hall* fails to teach or suggest immunizing an organism with recombinant N-terminal proBNP, as required by the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this reference. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Independent claims 130, 132, and 136 are directed to antibodies against recombinant N-terminal proBNP. As noted above, the antibodies described in *Hall* are produced against peptide fragments of N-terminal proBNP—not against recombinant N-terminal proBNP, as required by the claimed invention. Inasmuch as *Hall* fails to teach or suggest antibodies against recombinant N-terminal proBNP, as required by the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this reference. Accordingly, withdrawal of this ground of rejection is respectfully requested.

For at least the reasons set forth above, Applicants respectfully request withdrawal of all grounds of rejection.

Claim Rejections under 35 U.S.C. § 103

The rejection of claim 74 under 35 U.S.C. § 103(a) as being unpatentable over *Hall* in view of *Hunt et al.* (*Clin. Endocrinol.* **1997**, *47*, 287) has been rendered moot by cancellation of this claim. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 20-73 under 35 U.S.C. § 103(a) as being unpatentable over *Hall* in view of *Hunt et al.* has been obviated by amendment. Independent claim 20 has been amended to recite a lower detection limit for the N-terminal proBNP that is less than 1 fmol/ml of sample. This claimed lower detection limit is neither taught nor suggested in *Hall* or *Hunt et al.*

As noted above, *Hall* contains no teaching or suggestion of the lower detection limit required by the claimed invention. Whereas in the claimed invention, antibodies are produced against recombinant N-terminal proBNP, the immunoassays described in

Hall are performed using antibodies obtained by immunization of peptide fragments of N-terminal pro-BNP (e.g., amino acid fragments 1-21, 22-46, and 47-64) (e.g., col. 4, lines 30-41). The production of antibodies by means of peptide immunization results in antibodies that have poor affinity for the whole N-terminal proBNP molecule, which results in test procedures having significantly lower sensitivities than that required by the claimed invention (e.g., specification, page 4, first full paragraph; page 5, first full paragraph).

The claimed invention provides methods for identifying N-terminal proBNP via sandwich-type assays using first and second antibodies, and has a lower detection limit for N-terminal proBNP that is less than 1 fmol/ml of sample. In contrast, the examples described in *Hall* are limited to competitive assays having significantly lower sensitivity. For example, as described in the specification (e.g., page 5, first full paragraph), the competitive test performed in WO 93/24531 (the counterpart PCT publication to the cited *Hall* U.S. Patent) results in a lower detection limit of approximately 250 fmol/ml—about 250 times larger than that required by the claimed invention. This higher detection limit is neither sufficient for the differentiation of healthy individuals and patients suffering from heart failure nor for a differentiated classification of patient samples into the severity degrees of heart failure, as described in the specification (e.g., page 5, first full paragraph).

The claimed lower detection limit required by the claimed invention, which is neither taught nor suggested in *Hall*, is likewise neither taught nor suggested in *Hunt et al.* *Hunt et al.* describes that N-terminal proBNP (1-76) may be a more discerning marker of cardiac impairment than BNP-32 (77-108) (e.g., page 287, col. 2, last paragraph) and does not teach or suggest sandwich-type assays of the claimed invention. Moreover, *Hunt et al.* contains no teaching or suggestion of the lower detection limit required by the claimed invention. In contrast, *Hunt et al.* states that the detection limit for the competitive assay of N-terminal proBNP described therein is about 5.2 pmol/l, which corresponds to about 5.2 fmol/ml (e.g., paragraph bridging pages 289-290). This detection limit is more than five times higher than that required by the claimed invention. The most specific and sensitive assay for N-terminal proBNP described in *Hunt et al.* has a lower detection limit of 1.3 pmol/l (i.e., 1.3 fmol/ml), which

still exceeds the maximum value of the lower detection limit required by the claimed invention (page 293, second column, first full paragraph). Moreover, the sensitivities achieved in *Hunt et al.* require that complex extraction procedures be performed on the plasma samples prior to measurement (page 288, second column, first full paragraph). As described in the specification (e.g., page 5, second full paragraph), these complex extraction procedures may lead to the destruction of the analyte and errors in measurement.

Thus, inasmuch as the combination of *Hall* and *Hunt et al.* does not teach or suggest the lower detection limit required by the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 129-133, 136, and 139 under 35 U.S.C. § 103(a) as being unpatentable over *Hall* in view of *Hunt et al.* is respectfully traversed.

Independent claims 129 and 139 are directed to a method of producing antibodies against N-terminal proBNP and require "immunizing an organism with recombinant N-terminal proBNP" (emphasis added). As noted above, the method of producing antibodies described in *Hall* is based on immunizations with peptide fragments of N-terminal proBNP—not with recombinant N-terminal proBNP, as required by the claimed invention. Similarly, the method of producing an antiserum described in *Hunt et al.* is based on immunization of rabbits with a peptide fragment of amino acids 1-13 of human proBNP—not with recombinant N-terminal proBNP, as required by the claimed invention (page 288, second column, first full paragraph). Thus, inasmuch as the combination of *Hall* and *Hunt et al.* does not teach or suggest immunizing an organism with recombinant N-terminal proBNP, as required by the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Independent claims 130, 132, and 136 are directed to antibodies against recombinant N-terminal proBNP. As noted above, the antibodies described in *Hall* are

produced against peptide fragments of N-terminal proBNP—not against recombinant N-terminal proBNP, as required by the claimed invention. Similarly, as noted above, the antiserum described in *Hunt et al.* is based on immunization of rabbits with a peptide fragment of amino acids 1-13 of human proBNP—not with recombinant N-terminal proBNP, as required by the claimed invention. Inasmuch as the combination of *Hall* and *Hunt et al.* does not teach or suggest antibodies against recombinant N-terminal proBNP, as required by the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claim 74 under 35 U.S.C. § 103(a) as being unpatentable over *Hall* in view of *Hunt et al.* and further in view of *Seilhamer et al.* (WO 89/12069) and *Sudoh et al.* (*Biochem. Biophys. Res. Comm.* **1989**, *159*, 1427) has been rendered moot by cancellation of this claim. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 20-73 and 75-128 under 35 U.S.C. § 103(a) as being unpatentable over *Hall* in view of *Hunt et al.* and further in view of *Seilhamer et al.* and *Sudoh et al.* has been obviated by amendment. Independent claim 20 has been amended to recite a lower detection limit for the N-terminal proBNP that is less than 1 fmol/ml of sample. This lower detection limit is neither taught nor suggested in *Hall*, *Hunt et al.*, *Seilhamer et al.* or *Sudoh et al.*

As noted above, the claimed lower detection limit required by the claimed invention is neither taught nor suggested in *Hall* or *Hunt et al.*

Seilhamer et al. describes recombinant techniques for the production of natriuretic peptides and neither teaches nor suggests the claimed lower detection limit required by the claimed invention.

Sudoh et al. describes cloning and sequence analysis of cDNA encoding a precursor for human brain natriuretic peptide and neither teaches nor suggests the claimed lower detection limit required by the claimed invention.

Inasmuch as the combination of *Hall*, *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* does not teach or suggest the lower detection limit required by the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 129-133, 136, and 139 under 35 U.S.C. § 103(a) as being unpatentable over *Hall* in view of *Hunt et al.* and further in view of *Seilhamer et al.* and *Sudoh et al.* is respectfully traversed.

Independent claims 129 and 139 are directed to a method of producing antibodies against N-terminal proBNP and require "immunizing an organism with recombinant N-terminal proBNP" (emphasis added). However, none of the applied references teaches or suggests a method of production of recombinant proBNP (1-76). As noted above, neither *Hall* nor *Hunt et al.* teaches or suggests immunizing an organism with recombinant N-terminal proBNP, as required by the claimed invention. *Seilhamer et al.* describes a very long cDNA sequence of 1507 amino acids encoding porcine brain natriuretic peptide (e.g., Figure 1) and describes specific brain natriuretic peptides including porcine brain natriuretic peptide (pBNP; page 3) and a 6 amino acid N-terminal extended form of pBNP (e.g., page 4). However, *Seilhamer et al.* is completely silent with respect to the 76 amino acid N-terminal proBNP recited in the claimed methods. Moreover, while *Seilhamer et al.* carefully describes which portion of the sequence should be used to encode the 26 amino acid porcine brain natriuretic peptide (i.e., residues 660-723 and 1276-1289 inclusive; page 8), it neither teaches or suggests the recombinant N-terminal proBNP required by the claimed methods nor teaches or suggests which portions of the 1507 amino acid cDNA sequence described therein might be used to prepare such a recombinant N-terminal proBNP. *Sudoh et al.* is likewise silent with respect to the 76 amino acid N-terminal proBNP and contains no teaching or suggestion of the recombinant N-terminal proBNP required by the claimed methods. Inasmuch as the combination of *Hall*, *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* does not teach or suggest a recombinant N-terminal proBNP (1-76) as recited in the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this

combination of references. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Independent claims 130, 132, and 136 are directed to antibodies against recombinant N-terminal proBNP. As noted above, *Hall*, *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* are silent with respect to the recombinant N-terminal proBNP recited in the claimed invention. As a result, none of the applied references teaches or suggests antibodies against the recited recombinant N-terminal proBNP. Inasmuch as the combination of *Hall*, *Hunt et al.*, *Seilhamer et al.*, and *Sudoh et al.* does not teach or suggest antibodies against recombinant N-terminal proBNP, as required by the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of this combination of references. Accordingly, withdrawal of this ground of rejection is respectfully requested.

For at least the reasons set forth above, Applicants respectfully request withdrawal of all grounds of rejection.

New Claim:

New independent claim 141 is directed to methods of identifying N-terminal proBNP in a sample, and recites a lower detection limit for the N-terminal proBNP of less than 1 fmol/ml. As noted above, none of the applied references, alone or in combination, teaches or suggests the claimed lower detection limit. Accordingly, Applicants respectfully submit that new claim 141 is allowable.

Conclusion:

In view of the Amendment and Remarks set forth above, Applicants respectfully submit that the claimed invention is in condition for allowance. Early notification to such effect is earnestly solicited.

If for any reason the Examiner feels that the above Amendment and Remarks do not put the claims in condition to be allowed, and that a discussion would be helpful, it is respectfully requested that the Examiner contact the undersigned agent directly at (312)-321-4257.

Respectfully submitted,

Gregory Zayia
Registration No. 48,059
Agent for Applicants

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200